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High-Dose Chemotherapy and Hematopoietic Stem Cell Rescue for Breast Cancer: Experience in California

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ABSTRACT

The role of high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell rescue in breast cancer is still controversial. We analyzed the outcomes of 1111 consecutive patients with histologically proven breast cancer who underwent HDCT at 5 major California medical centers. The overall treatment-related mortality (TRM) was 2.3%. TRM was not influenced by disease stage or the HDCT regimen delivered, but it was influenced by hematopoietic graft source. The TRM was 6.1% when bone marrow with or without blood stem cells was used, but only 1.4% when blood stem cells alone were used ($P < .001$). With a median follow-up of 2.8 years (range, 0.1-8.2 years) after HDCT and autologous hematopoietic stem cell rescue, the estimated 5-year event-free survival (EFS) and overall survival (OS) for stage II/IIIA patients with ≥10 involved axillary lymph nodes were 67% and 76%, respectively. Patients with metastatic breast cancer (MBC) (median follow-up, 1.9 years [range, 0.03-8.3 years]) achieving a complete response (CR) to conventional-dose chemotherapy or rendered to a "no evidence of disease" status before HDCT had significantly better estimated 5-year EFS and OS (28% and 57%, respectively) than those achieving a partial response before HDCT (19% and 27%, respectively; $P \leq .0001$). Our data suggest that HDCT with hematopoietic stem cell rescue is safe and can be beneficial to patients with high-risk primary breast cancer and for those with MBC achieving CR/no evidence of disease.

KEY WORDS

High-dose chemotherapy • Breast cancer • California

INTRODUCTION

Breast cancer has been the most common indication for high-dose therapy and hematopoietic stem cell rescue in North America between 1993 and 1998 [1]. Despite this, outcomes of large series of breast cancer patients treated with high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell rescue are lacking. The largest publication of outcomes to date was from the North American Autologous Bone Marrow Transplant Registry (ABMTR) [1]. Although providing some insight into outcomes of HDCT for breast cancer, the North American ABMTR data are constrained by reporting bias and lack of subgroup analysis, such as stage II/IIIA patients with 10 or more involved axillary lymph nodes. This information has not resolved the controversies underlying HDCT for breast cancer [2-4]. Furthermore, the recent presentation of prospective, randomized trials comparing HDCT to conventional treatment has contributed to more confusion about the role of this treatment modality for breast cancer, owing in part to early reporting of the data [5-8]. We reasoned that the compilation and reporting of outcomes from a large series of breast cancer patients consecutively undergoing HDCT with long-lead follow-up times at 5 California bone marrow transplant centers would be of value in understanding the expected results of HDCT for breast cancer and would provide a basis to assess the HDCT arms of the prospective, randomized trials.

MATERIALS AND METHODS

Patients

We compiled raw data on 1111 consecutive breast cancer patients who underwent HDCT with autologous

Table 1. *Patient Accrual by Transplant Center**

Transplant Center	Total Patients	Disease Stage				
		II	IIIA	II/IIIA, ≥10 LN	IIIB	MBC
Alta Bates	127	21	24	34	21	61
Scripps	168	41	12	53	14	101
Stanford	217	73	39	100	15	90
UCLA	415	87	120	125	63	145
UCSF	184	54	36	85	21	73
Total	1111	276	231	397	134	470

*LN indicates involved axillary lymph nodes; MBC, metastatic breast cancer; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco.

hematopoietic stem cell rescue (bone marrow or peripheral blood) at 5 California bone marrow transplant centers (Table 1). The contributing institutions were Alta Bates Comprehensive Cancer Center (Berkeley), Scripps Clinic (La Jolla), Stanford University Medical Center (Stanford), University of California, Los Angeles School of Medicine (UCLA), and University of California, San Francisco (UCSF). These patients were all enrolled in phase 2 HDCT protocols approved by each center's Institutional Review Board, and each patient gave written, informed consent for their protocol treatment.

All patients had a histological diagnosis of breast cancer and were staged by the criteria of the American Joint Committee on Cancer [9]. All patients underwent standard recommended staging procedures [10] as well as radionuclide bone scintigraphy. Computer tomographic or magnetic resonance scans were done on areas of suspected or known metastases. There was no uniform practice for staging with bone marrow biopsies.

Eligibility for HDCT varied at each transplant center but uniformly included histological confirmation of breast cancer; written, informed consent; age <70 years; ambulatory performance status; adequate organ function (serum liver tests <3× that of each institution's upper limit, total bilirubin <2 mg/dL, serum creatinine <2 mg/dL, carbon monoxide diffusing capacity (DLCO) on pulmonary function testing ≥50% of predicted, and normal left ventricular ejection fraction by nuclear wall motion study or echocardiogram); lack of known bone marrow involvement with breast cancer; lack of significant comorbid medical or psychiatric illness; and insurance authorization. Eligibility was also stage-dependent (Table 1): (1) stage II with ≥10 involved axillary lymph nodes (LN); (2) stage IIIA; (3) stage IIIB (pre- or postmastectomy, with or without inflammatory changes); and (4) recurrent or metastatic breast cancer (MBC). MBC patients were eligible if they demonstrated a complete response (CR) or partial response (PR) to conventional-dose chemotherapy [11] or if they were rendered to a "no evidence of disease" (NED) status by surgery or radiation therapy. Previous treatment for MBC was not an exclusion.

Response criteria were fulfilled if the documented response lasted at least 4 weeks. For analysis purposes, NED patients were combined with CR patients. MBC patients with bone-only metastases were eligible if they demonstrated correction of hypercalcemia (if present), improvement in bone pain, and a reduction or stabilization in the size and/or number of bony lesions on radionuclide bone scintigraphy after conventional-dose chemotherapy.

Treatment

Except for some NED MBC patients, all patients received conventional-dose induction chemotherapy before HDCT. The conventional-dose regimen used and the number of cycles given varied depending on each institution's protocol(s). The source of autologous hematopoietic stem cells was pelvic bone marrow in 71 patients (6.3%), peripheral blood in 909 (81.7%), both in 44 (4.0%), and not reported in 90 (8.0%). Peripheral blood stem cells were mobilized according to each institution's protocol(s) using growth factors alone or in combination with chemotherapy. All institutions required a minimum of 2×10^6/kg $CD34^+$ cells or a minimum of 5×10^8/kg mononuclear cells to proceed to HDCT.

The HDCT regimen used varied at each transplant center (Table 2). STAMP I (CBP: cyclophosphamide, carmustine, cisplatin) [12] was the regimen of choice at both Stanford Uni-

Table 2. *High-Dose Chemotherapy Regimens by Transplant Center**

Transplant Center	CBP	CTM	CTCb	CT	Other
Alta Bates	0	122	0	4	1
Scripps	0	0	120	1	47
Stanford	133	21	3	51	9
UCLA	359	50	6	0	0
UCSF	0	150	7	0	27
Total	492	343	136	56	84

*CBP indicates cyclophosphamide, carmustine, cisplatin; CTM, cyclophosphamide, thiotepa, mitoxantrone; CTCb, cyclophosphamide, thiotepa, carboplatin; CT, cyclophosphamide, thiotepa; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco.

Table 3. *Treatment-Related Mortality Following High-Dose Chemotherapy**

	TRM, n	Total, n	TRM, %	P
All patients	25	1111	2.3	—
Graft source†				
Bone marrow	4	71	5.6	—
Bone marrow and blood	3	44	6.8	—
Blood	13	909	1.4	<.001
Stage				
II–III	11	641	1.7	—
MBC	14	470	3.0	<.1
HDCT regimen				
CBP	10	492	2.0	—
CTM	8	343	2.3	—
CTCb	1	136	0.7	—
CT	3	56	5.4	—
Other	3	84	3.6	>.25

*TRM indicates treatment-related mortality; MBC, metastatic breast cancer; HDCT, high-dose chemotherapy; CBP, cyclophosphamide, carmustine, cisplatin; CTM, cyclophosphamide, thiotepa, mitoxantrone; CTCb, cyclophosphamide, thiotepa, carboplatin; CT, cyclophosphamide, thiotepa.

†Excludes 87 patients (5 TRM) for whom the graft source was not reported.

versity and UCLA and accounted for 44.3% of all patients. CTM (cyclophosphamide, thiotepa, mioxantrone) [13] was the regimen of choice at Alta Bates and UCSF and accounted for 31.9% of all patients. STAMP V (CTCb: cyclophosphamide, thiotepa, carboplatin) [14] was the regimen of choice at Scripps and accounted for 12.2% of all patients. The CT regimen (cyclophosphamide, thiotepa) [15] (5.0%) and other regimens (6.6%) accounted for the remainder.

Patients with primary breast cancer received standard chest wall and axillary radiation therapy (including mastectomy patients) approximately 2 months after HDCT [16,17]. Some stage IIIB patients had mastectomy performed post-HDCT followed by radiation therapy. Primary breast cancer patients known to be positive for estrogen and/or progesterone receptor (or whose receptor status was unknown) received 5 years of tamoxifen (or other hormonal agent). Post-HDCT therapy for MBC patients was subject to the discretion of each transplant center and included no therapy, hormonal therapy, involved-field radiation therapy, and/or trastuzumab (Herceptin) therapy.

Statistical Considerations

The outcomes evaluated included: treatment-related mortality (TRM), event-free survival (EFS), and overall survival (OS). TRM was defined as any death related to HDCT but not due to breast cancer. There was no time limit as to when TRM could occur. TRM differences based on source of hematopoietic stem cells, stage of disease, and HDCT regimen were analyzed by the χ^2 contingency table method. The Kaplan-Meier estimates for EFS and OS were determined from the date of hematopoietic stem cell infusion using SurvMacro2 software (Dan Moore, Calico Computing) [18]. For EFS analysis, events included any deaths, relapse of breast cancer (local or distant), or first progression of breast cancer [19]. For OS analysis, events included death due to any cause [19]. All survival data were censored for patients without events at the date of last contact. Survival data were analyzed as of July 1, 1998, and presented as probabilities and 95% confidence intervals (CIs). Survival differences were analyzed by the Cox-Mantel log-rank method.

RESULTS

A total of 1111 breast cancer patients were treated with HDCT between November 20, 1978, and June 30, 1998. A total of 13 different HDCT regimens were used, but 1 of 3 regimens (CBP, CTM, and CTCb) was delivered to the vast majority of patients (87.4%) (Table 2). The overall TRM was 2.3% (Table 3). The TRM was significantly greater when bone marrow (with or without blood stem cells) was used (6.1%) than when blood stem cells alone were used (1.4%) as hematopoietic stem cell graft source (Table 3) ($P < .001$). There was no significant difference in TRM by patient stage or HDCT regimen (Table 3) ($P > .05$). When blood stem cells alone were used, there was no difference in TRM between stage II/III patients (1.2%) and MBC patients (1.8%) ($P > .25$).

With a median follow-up of 2.8 years (range, 0.1-8.2 years), the estimated 5-year EFS and OS for stage II/IIIA patients with ≥10 LN were 67% (95% CI, 60%-73%) and 76% (95% CI, 70%-81%), respectively (Table 4, Figure 1). There was no significant difference in EFS ($P = .59$) or OS ($P = .11$) for patients with ≥10 LN in stage II versus stage IIIA (Table 4; Figure 2). Stage IIIA patients with <10 LN (median follow-up 2.7 years [range, 0.1-7.2 years]) had survivals similar to those of stage IIIA patients with ≥10 LN (median follow-up, 2.0 years [range, 0.3-7.1 years]). The estimated 5-year EFS was 74% (95% CI, 61%-87%) versus 68% (95% CI, 57%-79%) ($P = .09$), respectively, and OS was 84% (95% CI, 76%-92%) versus 69% (95% CI, 55%-82%) ($P = .06$), respectively (Table 4). The median EFS has not been reached in the stage II and IIIA patients. The median OS is 8.1 years in both stage II and stage II/IIIA patients with ≥10 LN.

Stage IIIB patients, with a median follow-up of 1.9 years (range, 0.5-6.5 years), had an estimated 5-year EFS of 55% (95% CI, 41%-68%) and OS of 59% (95% CI, 4%2-75%), respectively (Table 4; Figure 1). The median EFS was 5.1 years, and OS was 5.9 years.

All patients with MBC (median follow-up, 1.9 years [range, 0.1-8.3 years]) had an estimated 5-year EFS of 29% (95% CI, 23%-35%) and OS of 40% (95% CI, 33%-46%) (Table 4; Figure 1). The median EFS for MBC patients was 1.4 years, and OS was 2.8 years. MBC patients entering

Table 4. *Survival After High-Dose Chemotherapy With Hematopoietic Stem Cell Rescue**

Disease Stage	n	5-Year Probability, % (95% CI)		Median, y		Follow-Up, y
		EFS	OS	EFS	OS	
II/IIIA, ≥10 LN	397	67 (60-73)	76 (70-81)	NR	8.1	2.8
II, ≥10 LN	276	66 (58-75)	78 (72-85)	NR	8.1	2.6
IIIA						
≥10 LN	121	68 (57-79)	69 (55-82)	NR	NR	2.0
<10 LN	111	74 (61-87)	84 (76-92)	NR	NR	2.7
All	232	71 (62-80)	76 (68-84)	NR	NR	2.3
IIIB	134	55 (41-68)	59 (42-75)	5.1	5.9	1.9
MBC						
All	457†	29 (22-35)	40 (33-46)	1.4	2.8	1.9
CR/NED	107	28 (10-47)	57 (42-73)	2.2	6.0	1.9
PR	205	19 (12-27)	27 (16-38)	1.0	2.0	1.3

*CI indicates confidence interval; EFS, event-free survival; OS, overall survival; LN, involved axillary lymph nodes; NR, not reached; MBC, metastatic breast cancer; CR/NED, complete response/no evidence of disease before HDCT; PR, partial response before HDCT.

†Includes 145 patients for whom no pre-HDCT disease status was reported.

HDCT in CR/NED (median follow-up 1.9 years [range, 0.1-7.1 years]) had significantly better outcomes than those entering HDCT in PR (median follow-up, 1.3 years [range, 0.1-6.4 years]), with median EFS of 2.2 and 1.0 years (P = .0001) and median OS of 6.0 and 2.0 years (P < .0001), respectively (Table 4; Figure 3).

A survival analysis was done on subgroups by stage according to the 3 most commonly used HDCT regimens, CBP, CTM, and CTCb (Table 5). Survival was estimated at 4 years rather than 5 because many subgroups of patients receiving CBP or CTCb had lead follow-ups of <5 years. In stage II/IIIA patients with ≥10 LN, EFS (P = .45) and OS (P = .19) were not significantly different among the 3 HDCT regimens (Table 5; Figures 4A and 5A). In no other stage II and IIIA subgroup was there a significant difference in EFS or OS among the 3 HDCT regimens examined (Table 5). Stage IIIB patients receiving CBP have EFS (P = .96) and OS (P = .08) rates similar to those of patients receiving CTM (Table 5; Figures 4B and 5B). Too few IIIB patients received CTCb for an adequate comparison.

In MBC patients as a whole, the EFS (P = .29) and OS (P = .053) were similar when the 3 regimens were analyzed by 3-way comparison (Table 5; Figures 4C and 5C). By pairwise comparison, CTCb appeared to be better than CBP (P = .02) and CTM (P = .02) in OS (Figure 5C) but was not statistically different than CBP or CTM in EFS (Figure 4C).

DISCUSSION

The data in this study represent one of the largest series of HDCT for breast cancer published to date, second only to that of the North American ABMTR [1]. Our series differs from that of the North American ABMTR by virtue of consecutive patients being analyzed, more uniform therapy given in a small number of institutions, longer lead follow-up, and more detailed analysis of TRM and subgroup outcomes.

Our overall TRM (2.3%) was lower than that reported by the North American ABMTR (7.7%) [1]. This is likely because a greater proportion of our patients (88.8%) received blood stem cell grafts rather than bone marrow grafts (with or without blood stem cells) compared with the North American ABMTR (42.6%). We were able to demonstrate that the source of hematopoietic stem cells influenced TRM (significantly less TRM when blood stem

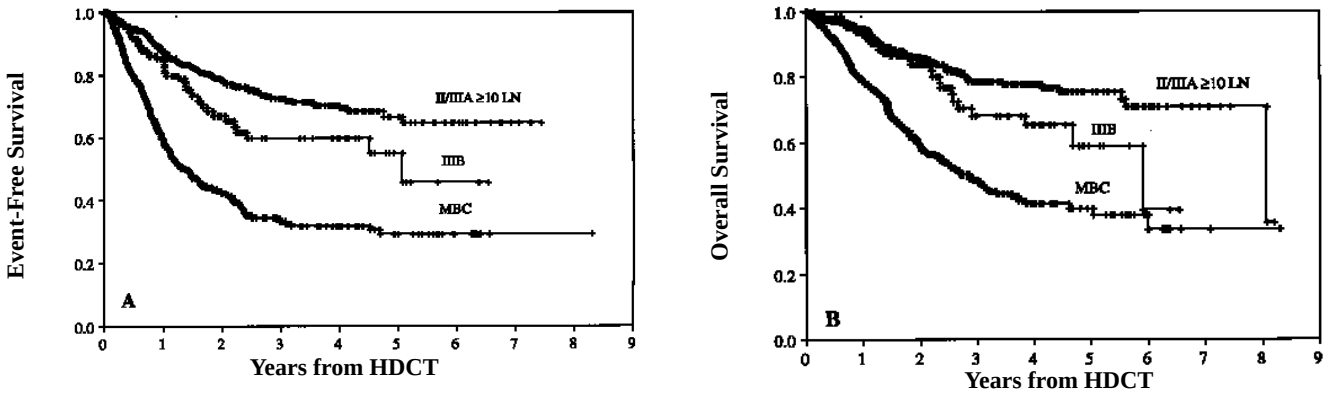

Figure 1. Survival of breast cancer patients undergoing high-dose chemotherapy (HDCT). Event-free survival (A) and overall survival (B) are shown according to breast cancer stage. LN indicates lymph nodes; MBC, metastatic breast cancer.

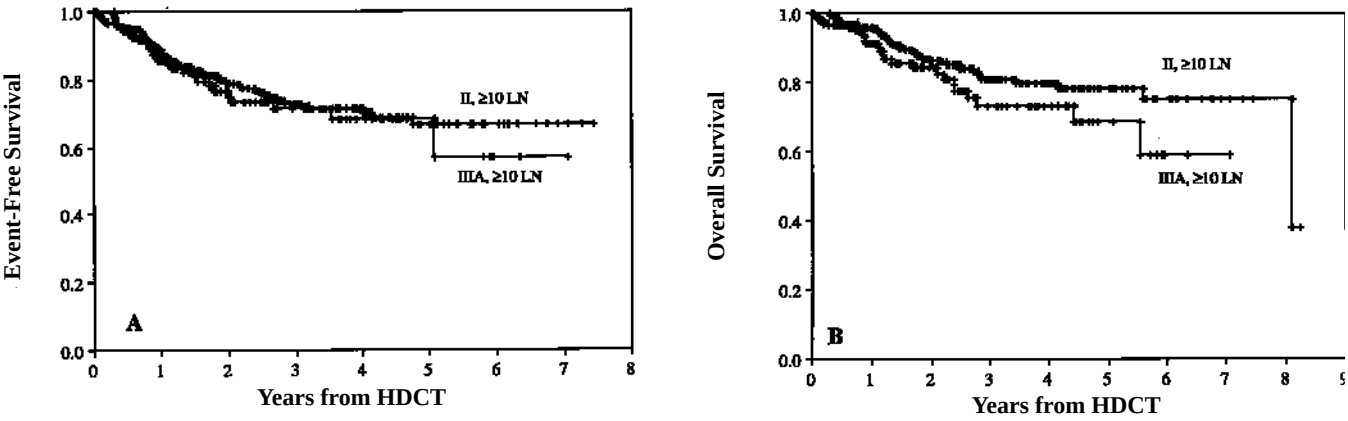

Figure 2. Survival of primary breast cancer patients with ≥10 axillary lymph nodes (LN) undergoing high-dose chemotherapy (HDCT). The event-free survival (EFS) (A) and overall survival (OS) (B) of stage II/IIIA breast cancer patients with ≥10 LN are shown according to stage of disease. There was no difference in EFS (P = .59) or OS (P = .11) between the 2 stages by log-rank analysis.

cells were used alone), whereas patient disease stage and HDCT regimen did not. A significantly lower TRM when blood rather than bone marrow is used as hematopoietic stem cell grafts after HDCT has been previously demonstrated in lymphoma [20] and has been the primary explanation for a trend in decreasing TRM in HDCT for breast cancer in North America. Unlike our series, primary breast cancer patients had a lower TRM (3%) than metastatic patients (10%) in the North American AMBTR report.

Blood stem cell rescue after HDCT is thought to reduce TRM by shortening the period of neutropenia, facilitating the recovery of mucosal damage, and decreasing the incidence of veno-occlusive disease of the liver [21]. One might expect the same benefit, however, when blood stem cells are added to bone marrow grafts. In our series, the combination of bone marrow and blood stem cells had a TRM similar to bone marrow alone. The most likely explanation is that in our study the combining of stem cell grafts was not done as a deliberate procedure but rather that bone marrow was added to blood stem cells in patients who failed to mobilize adequate numbers of stem cells alone for HDCT rescue. Such patients demonstrate engraftment kinetics more resembling bone marrow rescue than blood stem cell rescue [13]. When bone marrow is deliberately combined with blood stem cells, hematopoietic recovery is fast and resembles blood stem cell–only engraftment [12]. Paradoxically, rapid hematopoietic engraftment following deliberately combined bone marrow and blood stem cell rescue did not reduce the TRM in the recent Cancer and Leukemia Group B (CALGB)-led Intergroup trial (CALGB 9082/SWOG 9114/NCIC MA-13) comparing CBP with hematopoietic stem cell rescue to intermediate-dose CBP in primary breast cancer patients with ≥10 LN [7]. The TRM following CBP was 7.3% and thought to be a consequence of treatment-induced interstitial pneumonitis and hemolytic-uremic syndrome [12,22]. The TRM with CBP was lower (2.0%) in our 492 patients who received CBP. In California, CBP was the HDCT regimen of choice at 2 centers and was the most common HDCT regimen delivered in our series. The experience with CBP at these 2 centers produced a low TRM. The Intergroup trial [7] showed a trend toward reduced TRM at centers performing >50 transplantations during the course of the study, which likely explains the low TRM in our series. The Intergroup trial involved many more transplantation sites with

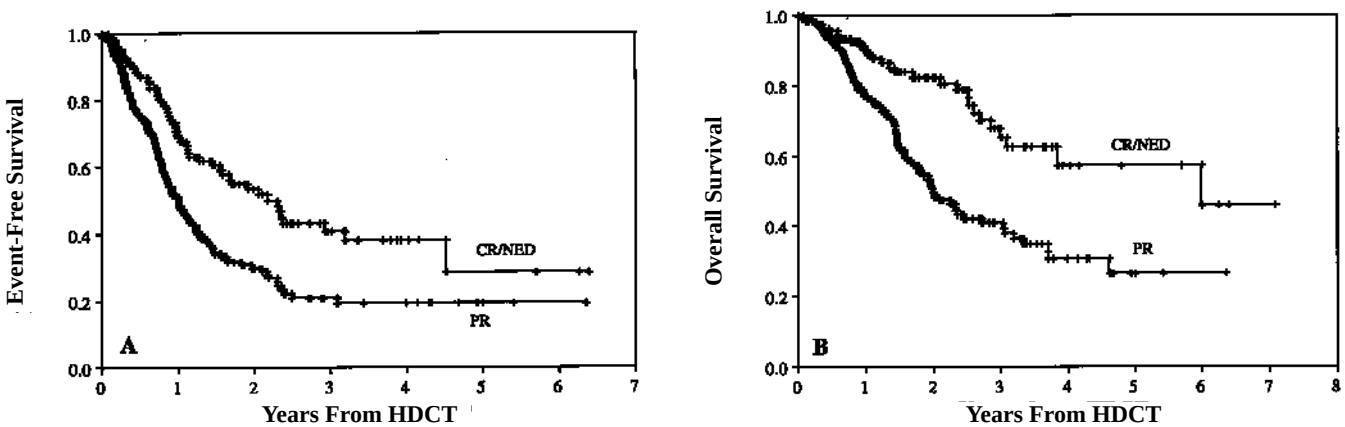

Figure 3. Survival of metastatic breast cancer (MBC) patients undergoing high-dose chemotherapy (HDCT). The event-free survival (EFS) (A) and overall survival (OS) (B) of patients with MBC are shown according to disease status at time of HDCT (complete response/no evidence of disease [CR/NED] vs. partial response [PR]). CR/NED patients had better EFS (P = .0001) and OS (P < .0001) than did PR patients by log-rank analysis.

Table 5. *Survival After High-Dose Chemotherapy With Hematopoietic Stem Cell Rescue by Regimen**

	4-Year Probabilities, % (95% CI)								
	CBP			CTM			CTCb		
Stage	n	EFS	OS	n	EFS	OS	n	EFS	OS
II/IIIA, ≥10 LN	174	77 (68-85)	86 (80-93)	129	68 (58-77)	75 (66-84)	46	78 (63-94)	87 (75-99)
II, ≥10 LN	113	79 (70-88)	90 (84-96)	84	66 (53-79)	76 (64-87)	36	77 (59-96)	93 (85-100)
IIIA									
≥10 LN	61	70 (51-89)	77 (61-92)	45	71 (56-86)	74 (58-89)	10	79 (53-100)	69 (32-100)
All	146	70 (57-83)	81 (72-89)	62	73 (60-86)	78 (66-91)	16	86 (68-100)	77 (54-100)
IIIB	70	58 (43-74)	72 (55-89)	43	59 (42-76)	52 (33-71)	11	—	—
MBC, all	162	38 (27-48)	41 (29-53)	148	28 (19-36)	37 (17-46)	64	40 (23-53)	67 (51-83)

*CI indicates confidence interval; CBP, cyclophosphamide, carmustine, cisplatin; CTM, cyclophosphamide, thiotepa, mitoxantrone; CTCb, cyclophosphamide, thiotepa, carboplatin; EFS, event-free survival; OS, overall survival; LN, involved axillary lymph nodes; MBC, metastatic breast cancer.

less CBP experience and hence a higher TRM than expected (1-3%) [7]. A surprising finding in our study was that the HDCT regimen used did not impact TRM. Our observations suggest that centers experienced with CBP will generate TRM rates no different from those of other HDCT regimens.

Of particular interest over the past decade has been the use of HDCT for primary breast cancer with ≥10 LN. The survival analysis of such patients was lacking in the North American ABMTR report [1]. Experience at several centers involving 18 to 85 patients each has been published, with estimated 5-year EFS ranging from 50% to 64% (follow-up range, 2.7-5.0 years) [7,13,23-25]. The previously mentioned Intergroup trial randomized 394 patients to CBP, had a median follow-up of 3 years, and did not report 5-year EFS or OS [7]. The analysis of the Intergroup trial is considered to be preliminary. Our series of patients with ≥10

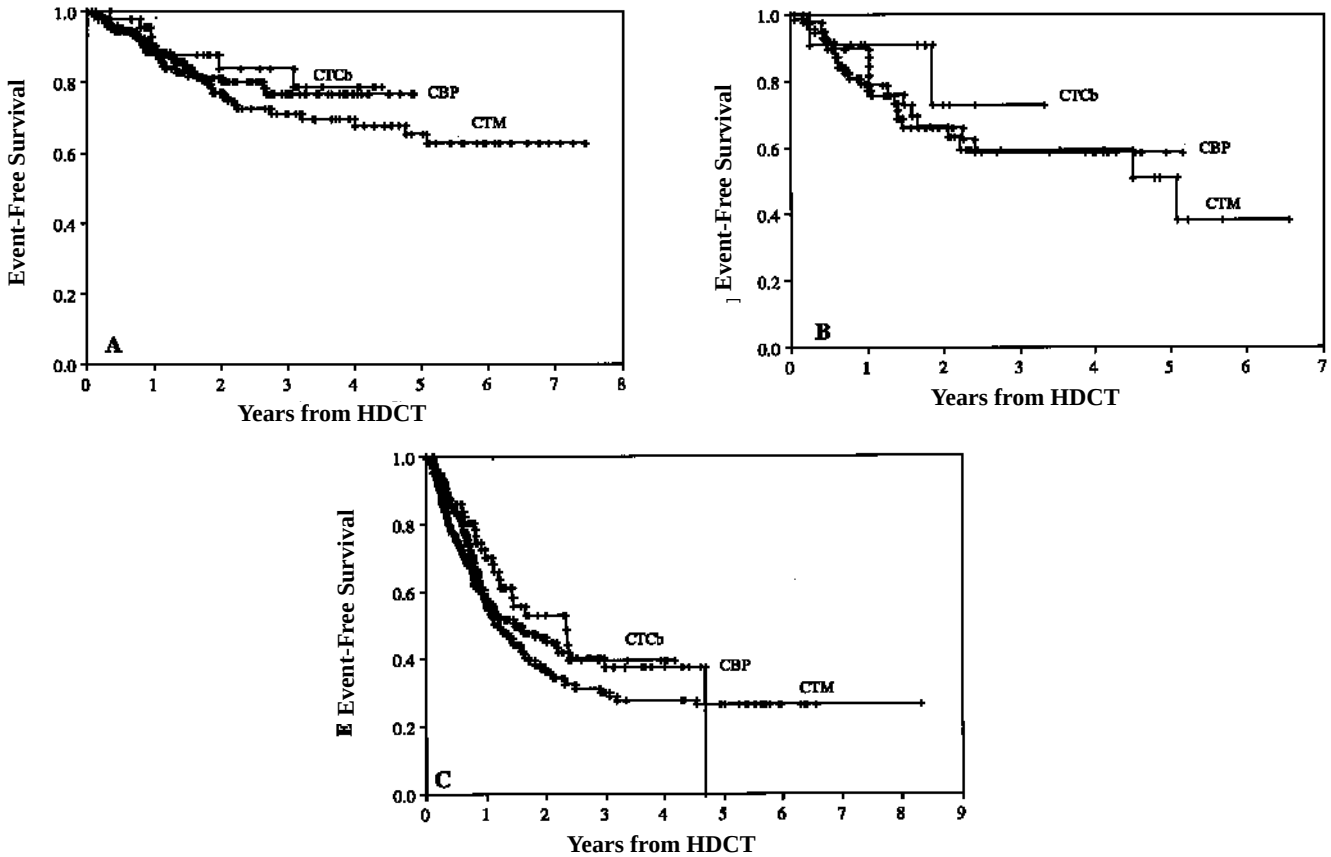

Figure 4. Event-free survival (EFS) of breast cancer patients undergoing high-dose chemotherapy (HDCT) according to regimen. The EFS of breast cancer patients is shown according to the following 3 HDCT regimens: CTCb (cyclophosphamide, thiotepa, carboplatin), CBP (cyclophosphamide, carmustine, cisplatin), and CTM (cyclophosphamide, thiotepa, mioxantrone). A, Stage II/IIA with ≥10 involved axillary lymph nodes. B, Stage IIIB. C, Metastatic breast cancer. There was no difference in EFS in any stage by log-rank analysis done by 3-way comparison or by pair-wise comparisons.

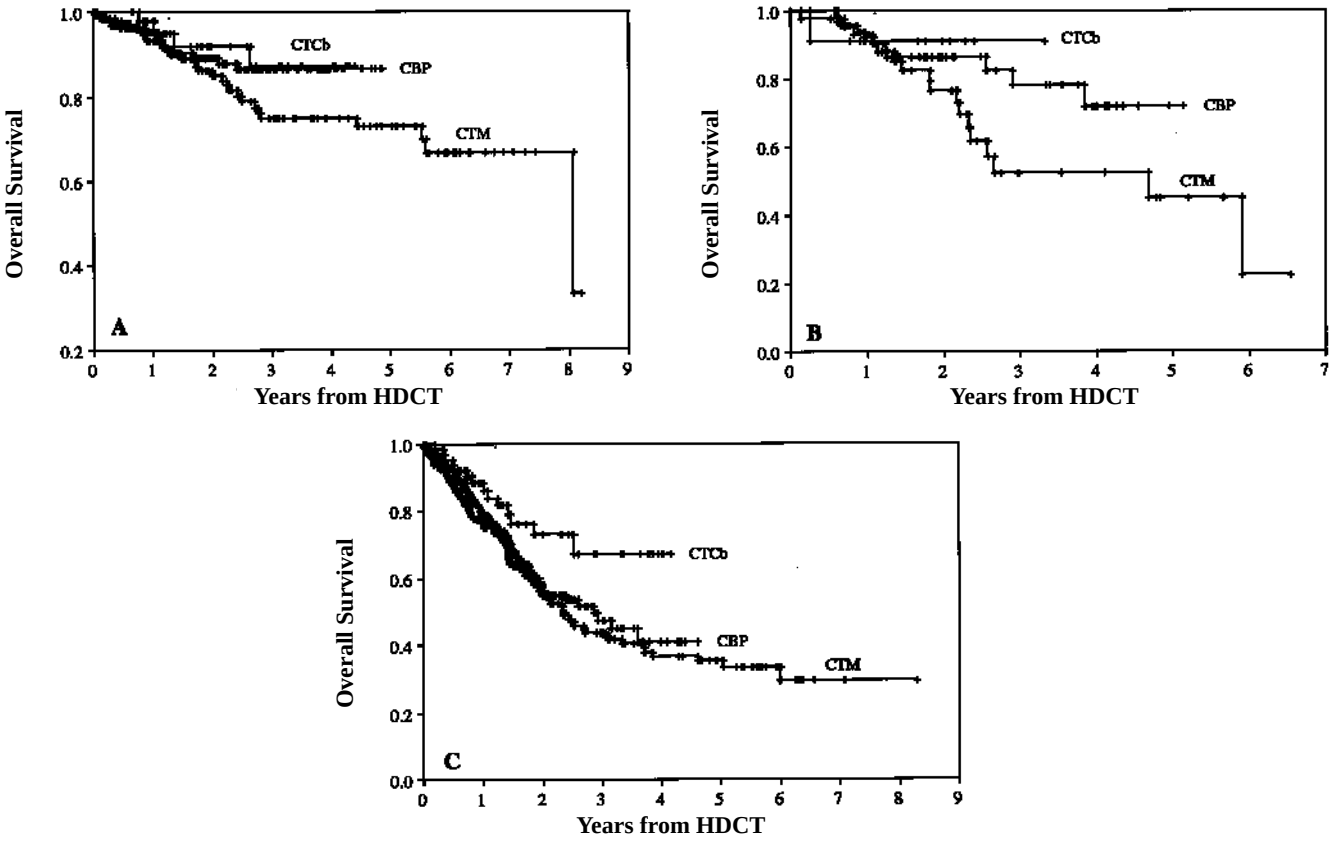

Figure 5. Overall survival (OS) of breast cancer patients undergoing high-dose chemotherapy (HDCT) according to regimen. The OS of breast cancer patients is shown according to the following 3 HDCT regimens: CBP (cyclophosphamide, carmustine, cisplatin), CTCb (cyclophosphamide, thiotepa, carboplatin), and CTM (cyclophosphamide, thiotepa, mioxantrone). A, Stage II/IIIA with ≥10 involved axillary lymph nodes (LNs). B, Stage IIIB. C, Metastatic breast cancer (MBC). There was no difference in OS in stage II/IIIA with ≥10 LNs or in stage IIIB patients by log-rank analysis done by 3-way or by pair-wise comparisons. There was no difference in OS in MBC patients by log-rank 3-way comparison (P = .053), but CTCb was better than CBP (P = .02) and CTM (P = .02) by log-rank pair-wise comparisons.

LN is virtually identical to the Intergroup study experimental arm in number (397) and median follow-up (2.8 years). With a range of follow-up from 0.1 to 8.2 years and 42 patients more than 5 years from hematopoietic stem cell rescue, the estimated 5-year EFS and OS in our stage II/IIIA patients with ≥10 LN are 67% and 76%, respectively. This result compares favorably to 5-year relapse-free survivals of 17% to 56% (weighted mean, 38%) in such patients receiving conventional-dose adjuvant chemotherapy with follow-ups ranging from 3.3 to 10.3 years [4,7,23,26-37]. Comparisons of outcomes with HDCT to historical outcomes with conventional-dose chemotherapy must be interpreted with caution. Factors such as patient selection, differences in supportive care, and length of follow-up preclude our ability to draw definitive conclusions. Nevertheless, reported survivals for HDCT are consistently higher than conventional-dose chemotherapy in high-risk primary breast cancer patients.

In this study, we were able to support previous observations that stage IIIA patients (with or without ≥10 LN) did as well as stage II patients after HDCT [1,25]. We did not have the primary data to confirm or refute other previously described prognostic variables in primary breast cancer patients undergoing HDCT, including hormone receptor status, primary tumor size, and the ratio of number of involved axillary LN to the total number of LN sampled [13,25,38]. Our data suggest a benefit of HDCT over conventional chemotherapy in primary breast cancer patients with ≥10 LN. Encouraging results in the ≥10 LN patients have led to the exploration of HDCT in stage II/IIIA patients with 4 to 9 LN [39].

Our stage-IIIB patients included a mixture of those with clinical inflammatory breast cancer and those without clinical inflammatory breast cancer but who met pathologic criteria for stage IIIB disease. With a range of follow-up of 0.5 to 6.5 years (median, 1.9 years) and 6 patients more than 5 years from hematopoietic stem cell rescue, the 5-year estimated EFS and OS were 55% and 59%, respectively. This outcome is similar to that of 30 IIIB patients undergoing HDCT at the University of Colorado (estimated 4-year EFS 62% and OS 83%) [40] and appears to be better than that observed from "inflammatory" patients reported to the North American ABMTR whose 4-year progression-free survival (PFS) and OS were approximately 40% and 46%, respectively [1]. Overall, the HDCT survival data from these analyses, including ours, appear better than those for "inflammatory" patients receiving conventional-dose chemotherapy (weighted average 5-year PFS 34%, range

10-54%) [41]. Whether all "inflammatory" patients reported to the North American ABMTR were truly "inflammatory" or a mixture including both inflammatory and noninflammatory stage IIIB patients is unclear. This distinction is important because a series of inflammatory-only stage IIIB patients would be expected to do worse than a series of mixed-stage IIIB patients.

Patients with MBC undergoing HDCT are notable for having heterogeneous disease. Although some clinical trials of HDCT have reduced heterogeneity by restricting inclusion only to those individuals responding to their first course of chemotherapy for metastatic disease [5,42,43] or to those receiving no prior chemotherapy for metastatic disease [44,45], others (including this California series) have not [1,14]. Presumably, patients responding to their first course of chemotherapy for metastatic disease will fare better than those failing their first course [46]. Other variables known to predict survival outcomes following HDCT for MBC include age, performance status, tumor grade, hormone receptor status, *her2/neu* overexpression, use of tamoxifen in the adjuvant setting, number of metastatic organ sites, organ distribution of metastasis, time from initial breast cancer diagnosis, whether previous adjuvant chemotherapy was administered, use of post-HDCT radiotherapy, and the degree of response to conventional-dose chemotherapy before HDCT [47-54]. The large number of prognostic variables reflects the heterogeneity of MBC and makes comparisons between phase 2 trials problematic.

In our series, we were able to confirm that disease status before HDCT is prognostic for outcome, as previously shown [1,14,42,49]. Our patients achieving CR/NED before HDCT did particularly well, with an estimated 5-year EFS and OS of 28% and 57%, respectively. Their median EFS and OS were 2.2 and 6.0 years, respectively (Table 4). Two other studies of HDCT in patients with minimal disease (NED by surgery or radiation, <5% bone marrow involvement as the only site of metastatic disease, or stage IV by virtue of only supraclavicular LN involvement) have shown median EFSs of 2.6 and 3.6 years and median OSs of 3.0 and 6.4 years [52,55]. These outcomes appear to be better than those reported for 263 patients with MBC at the M.D. Anderson Cancer Center who achieved CR with conventional-dose chemotherapy but did not receive HDCT intensification. Their median EFS and OS were 1.8 and 3.5 years, respectively [46]. Again, comparison must be interpreted with caution because the median follow-up in our series (1.9 years) is much shorter than in the M.D. Anderson series (median follow-up, 6.3 years). On the other hand, the M.D. Anderson patients had previously untreated MBC and therefore were more likely to have responsive disease and more favorable survivals. Many of our MBC patients had been previously treated and therefore had more unfavorable prognoses. Furthermore, survival for conventionally treated MBC patients is determined from the date of commencement of first therapy, whereas survival for MBC patients undergoing HDCT is determined from the date of stem cell transplantation, skewing survival in favor of conventionally treated patients.

The observation of more favorable outcomes with HDCT in CR/NED patients may be important. A recent large (n = 199), prospective, randomized trial of HDCT using CTCb versus conventional-dose maintenance chemotherapy in patients with MBC responding to conventional-dose induction chemotherapy found no difference in OS between randomized groups [5]. However, this study had insufficient numbers of CR patients before randomization (n = 56) to exclude the possibility of benefit from HDCT for MBC patients with minimal disease [5]. Whether HDCT for MBC patients with minimal disease is superior to conventional-dose treatment remains uncertain.

An unanswered question is whether a particular HDCT regimen influences outcome. A multivariate analysis from the North American ABMTR found that HDCT regimens had no influence on treatment failure for women with MBC [49]. HDCT regimens for breast cancer have not been compared in a controlled fashion to date. Our uncontrolled comparison of outcomes with CBP, CTM, and CTCb found no difference in TRM based on the HDCT regimen delivered (Table 3). Further, we could not find any significant differences in EFS or OS in any stage subgroups comparing the 3 regimens. Because of the relatively small numbers within the subgroups analyzed, we had the power to detect only large differences in outcomes. In addition, because each center used predominantly 1 HDCT regimen, differences in patients' prognostic characteristics between centers could have inherently biased outcomes. Thus, our analysis is insufficient to exclude possible differences in outcome related to the HDCT regimen. If outcome differences exist between HDCT regimens, they will likely be small and may depend on other factors, such as type of prior conventional-dose therapy. Only large, prospective randomized trials will be able to definitively determine whether the HDCT regimen administered influences survival outcomes.

In conclusion, our analysis of a large number of consecutive breast cancer patients who underwent HDCT supports the contention that the role of HDCT in treating this disease is far from settled. Outcomes in stage II/IIIA disease with ≥10 LN appear to be better than those in historical patients who received conventional-dose adjuvant chemotherapy in this setting. The use of peripheral blood stem cells is associated with a low TRM, making this therapy routinely applicable in the high-risk primary breast cancer setting. Furthermore, based on comparison with historical controls, our outcome data cannot exclude the possibility of benefit from HDCT intensification in patients with MBC achieving a minimal disease status.

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REFERENCES

1. Antman K, Rowlings PA, Vaughan WP, et al. High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. *J Clin Oncol.* 1997;15:1870-1879.
2. Rahman ZU, Frye DK, Buzdar AU, et al. Impact of selection process on response rate and long-term survival of potential high-dose chemotherapy candidates treated with standard-dose doxorubicin containing chemotherapy in patients with metastatic breast cancer. *J Clin Oncol.* 1997;15:3171-3177.

3. Gradishar WJ, Tallman MS, Abrams JS. High-dose chemotherapy for breast cancer. *Ann Intern Med*. 1996;125:599-604.
4. Garcia-Carbenero R, Hidalgo M, Paz-Ares L, et al. Patient selection in high-dose chemotherapy trials: relevance in high-risk breast cancer. *J Clin Oncol*. 1997;15:3178-3184.
5. Stadtmauer EA, O'Neill A, Goldstein LJ, et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. *N Engl J Med*. 2000;342:1069-1076.
6. Lotz J-P, Cure H, Janvier M, et al. High-dose chemotherapy (HD-CT) with hematopoietic stem cell transplantation (HSCT) for metastatic breast cancer (MBC): results of the French protocol PEGASE 04 [abstract]. *Proc Am Soc Clin Oncol*. 1999;18:43a. Abstract 161.
7. Peters W, Rosner G, Vrendenburgh J, et al. A prospective, randomized comparison of two doses of combination alkylating agents (AA) as consolidation after CAF in high-risk primary breast cancer involving ten or more axillary lymph nodes (LN): preliminary results of CALGB 9082/SWOG 9114/NCIC MA-13 [abstract]. *Proc Am Soc Clin Oncol*. 1999;18:1a. Abstract 2.
8. The Scandinavian Breast Cancer Study Group 9401. Results from a randomized adjuvant breast cancer study with high dose chemotherapy with CTCb supported by autologous bone marrow stem cells versus dose escalated and tailored FEC therapy [abstract]. *Proc Am Soc Clin Oncol*. 1999;18:2a. Abstract 3.
9. Beahrs OH, Henson DE, Hutter RVP, Myers MH, eds. *Manual for Staging of Cancer*. Philadelphia, PA: J.B.Lippincott; 1988:145.
10. Update: NCCN practice guidelines for the treatment of breast cancer: National Comprehensive Cancer Network Proceedings. *Oncology*. 1999;13:41-66.
11. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.
12. Peters WP, Ross M, Vredenburgh JJ, et al. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol*. 1993;11:1132-1143.
13. Damon LE, Wolf JL, Rugo HS, et al. High-dose chemotherapy (CTM) for breast cancer. *Bone Marrow Transplant*. 2000;26:257-268.
14. Antman K, Ayash L, Elias A, et al. A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. *J Clin Oncol*. 1992;10:102-110.
15. Williams SF, Mick R, Desser R, Golick J, Beschorner J, Bitran JD. High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer. *J Clin Oncol*. 1989;7:1824-1830.
16. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy: Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med*. 1997;337:949-955.
17. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med*. 1997;337:956-962.
18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
19. Cheson BD, Horning SJ, Coiffer B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas [review]. *J Clin Oncol*. 1999;17:1244-1253.
20. Chao NJ, Schriber JR, Grimes K, et al. Granulocyte colony-stimulating factor "mobilized" peripheral blood progenitor cells accelerate granulocyte and platelet recovery after high-dose chemotherapy. *Blood*. 1993;81:2031-2035.
21. Fisher DC, Vrendenburgh JJ, Petros WP, et al. Reduced mortality following bone marrow transplantation for breast cancer with the addition of peripheral blood progenitor cells is due to a marked reduction in veno-occlusive disease of the liver. *Bone Marrow Transplant*. 1998;21:117-122.
22. Todd NW, Peters WP, Ost AH, Roggli VL, Piantadosi CA. Pulmonary drug toxicity in patients with primary breast cancer treated with high-dose combination chemotherapy and autologous bone marrow transplantation. *Am Rev Respir Dis*. 1993;147:1264-1270.
23. Gianni AM, Siena S, Bregni M, et al. Efficacy, toxicity, and applicability of high-dose sequential chemotherapy as adjuvant treatment in operable breast cancer with 10 or more involved axillary lymph nodes: five-year results. *J Clin Oncol*. 1997;15:2312-2321.
24. Tajita T, Tokuda J, Ohta M, Kubota M, Mitomi T. Role of autologous bone marrow transplantation in cancer chemotherapy. *Low Temp Med*. 1989;5:44-50.
25. Somlo G, Doroshow JH, Forman S, et al. High-dose chemotherapy and stem-cell rescue in the treatment of high-risk breast cancer: prognostic indicators of progression-free and overall survival. *J Clin Oncol*. 1997;15:2882-2893.
26. Jones SE, Moon TE, Bonadonna G, et al. Comparison of different trials of adjuvant chemotherapy in stage II breast cancer using a natural history data base. *Am J Clin Oncol*. 1987;10:387-395.
27. Moon TE, Jones SE, Bonadonna G, et al. Development and use of a natural history data base of breast cancer studies. *Am J Clin Oncol*. 1987;10:396-403.
28. Abeloff MD, Beveridge RA, Donehower RC, et al. Sixteen-week dose-intense chemotherapy in the adjuvant treatment of breast cancer. *J Natl Cancer Inst*. 1990;82:570-574.
29. Davidson NE, Abeloff MD. Adjuvant systemic therapy in women with early-stage breast cancer at high risk for relapse. *J Natl Cancer Inst*. 1992;84:301-305.
30. Kaufman M, Jonat W, Caffier H, et al. Adjuvant systemic risk adapted cytotoxic ± tamoxifen therapy in women with node positive breast cancer. In: Salmon S, ed. *Adjuvant Therapy of Cancer V*. Orlando, FL: Grune & Stratton; 1987:337-346.
31. Clark GM, McGuire WL. New biologic prognostic factors in breast cancer. *Oncology*. 1989;3:49-54.
32. Buzzoni R, Bonadonna G, Valagussa P, Zambetti M. Adjuvant chemotherapy with doxorubicin plus cyclophosphamide, methotrexate, and fluorouracil in the treatment of resectable breast cancer with more than three positive axillary nodes. *J Clin Oncol*. 1991;9:2134-2140.
33. Bonadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes: ten year results. *JAMA*. 1995;273:542-547.
34. Buzdar AV, Kau S-W, Hortobagyi GN, et al. Clinical course of patients with breast cancer with ten or more positive nodes who were treated with doxorubicin-containing adjuvant therapy. *Cancer*. 1992;69:448-452.
35. Gilchrist KW, Gray R, Fowble B, Tormey DC, Taylor SG IV. Tumor necrosis factor is a prognostic predictor for early recurrence and death in lymph-node positive breast cancer: a 10-year follow-up study of 728 Eastern Cooperative Oncology Group patients. *J Clin Oncol*. 1993;10:1919-1935.
36. Spaeth D, Luprosi E, Weber B, et al. High-risk primary breast cancer (PBC) with 10 or more positive axillary lymph nodes (PALN): a 163 patients (pts) series [abstract]. *Proc Am Soc Clin Oncol*. 1994;13:106. Abstract 226.

37. Ung O, Langlands AO, Barraclough B, Boyages J. Combined chemotherapy and radiotherapy for patients with breast cancer and extensive nodal involvement. *J Clin Oncol*. 1995;13:435-443.
38. Nieto Y, Cagnoni PJ, Shpall EJ, et al. A predictive model for relapse in high-risk primary breast cancer patients treated with high-dose chemotherapy and autologous stem-cell transplant. *Clin Cancer Res*. 1999;5:3425-3431.
39. Bearman SI, Overmoyer BA, Bolwell BJ, et al. High-dose chemotherapy with autologous peripheral blood progenitor cell support for primary breast cancer in patients with 4-9 involved axillary lymph nodes. *Bone Marrow Transplant*. 1997;20:931-937.
40. Cagnoni PJ, Nieto Y, Shpall EJ, et al. High-dose chemotherapy with autologous hematopoietic progenitor-cell support as part of combined modality therapy in patients with inflammatory breast cancer. *J Clin Oncol*. 1998;16:1661-1668.
41. Jaiyesimi JA, Buzdar AV, Hortobagyi G. Inflammatory breast cancer: a review. *J Clin Oncol*. 1992;10:1014-1024.
42. Ayash LJ, Elias A, Wheeler C, et al. Double dose-intensive chemotherapy with autologous marrow and peripheral blood progenitor-cell support for metastatic breast cancer: a feasibility study. *J Clin Oncol*. 1994;12:37-44.
43. Peters WP, Jones RB, Vredenburgh J, et al. A large, prospective, randomized trial of high-dose combination alkylating agents (CPB) with autologous cellular support (ABMS) as consolidation for patients with metastatic breast cancer achieving complete remission after intensive doxorubicin-based induction chemotherapy (AFM) [abstract]. *Proc Am Soc Clin Oncol*. 1996;15:121. Abstract 149.
44. Peters WP, Schpall EJ, Jones RB, et al. High-dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. *J Clin Oncol*. 1988;6:1368-1376.
45. Bezwoda WR, Seymor L, Dansey RD. High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. *J Clin Oncol*. 1995;13:2483-2489.
46. Greenberg PAC, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol*. 1996;14:2197-2205.
47. Ayash LJ, Wheeler C, Fairclough D, et al. Prognostic factors for prolonged progression-free survival with high-dose chemotherapy with autologous stem cell support for MBC. *J Clin Oncol*. 1995;13:2043-2049.
48. Dunphy FR, Spitzer G, Rossiter Fornoff JE, et al. Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support. *Cancer*. 1994;73:2157-2167.
49. Rowlings PA, Williams SF, Antman KH, et al. Factors correlated with progression-free survival after high-dose chemotherapy and hematopoietic stem cell transplantation for metastatic breast cancer. *JAMA*. 1999;282:1335-1343.
50. Bewick M, Chadderton T, Conlon M, et al. Expression of C-erb/HER-2 in patients with metastatic breast cancer undergoing high-dose chemotherapy and autologous blood stem cell support. *Bone Marrow Transplant*. 1999;24:377-384.
51. Rizzieri DA, Vredenburgh JJ, Jones R, et al. Prognostic and predictive factors for patients with metastatic breast cancer undergoing aggressive induction therapy followed by high-dose chemotherapy with autologous stem-cell support. *J Clin Oncol*. 1999;17:3064-3074.
52. Nieto Y, Cagnoni PJ, Shpall EJ, et al. Phase II trial of high-dose chemotherapy with autologous stem cell transplant for stage IV breast cancer with minimal metastatic disease. *Clin Cancer Res*. 1999;5:1731-1737.
53. Carter DL, Marks LB, Bean JM, et al. Impact of consolidation radiotherapy in patients with advanced breast cancer treated with high-dose chemotherapy and autologous bone marrow rescue. *J Clin Oncol*. 1999;17:887-893.
54. Laport GF, Grad G, Grinblatt DL, Bitran JD, Williams SF. High-dose chemotherapy consolidation with autologous stem cell rescue in metastatic breast cancer: a 10-year experience. *Bone Marrow Transplant*. 1998;21:127-132.
55. Abraham R, Nagy T, Goss PE, Crump M. High dose chemotherapy and autologous blood stem cell support in women with breast carcinoma and isolated supraclavicular lymph node metastases. *Cancer*. 2000;88:790-795.